TUMEURS GERMINALES

Emmanuel Seront, MD PhD

Jean Pascal Machiels, MD PhD

Department of Medical Oncology

Institut Roi Albert II

Cliniques universitaires Saint-Luc

Université catholique de Louvain, Brussels, Belgium

INSTITUT
ROI ALBERT II
CANCÉROLOGIE ET HÉMATOLOGIE
Cliniques universitaires SAINT-LUC | UCL Bruxelles

Epidemiology

- Germ cell tumours are rare malignancy
- The most common cancer in caucasian young men (aged 15-40y).

- 50% are pure seminomas and 50% are non-seminomas.

- 5% outside of the gonads
- 2-3% of testicular cancer are bilateral

Cure rate approximately 100% in stage I and exceed 80 in metatatic stage

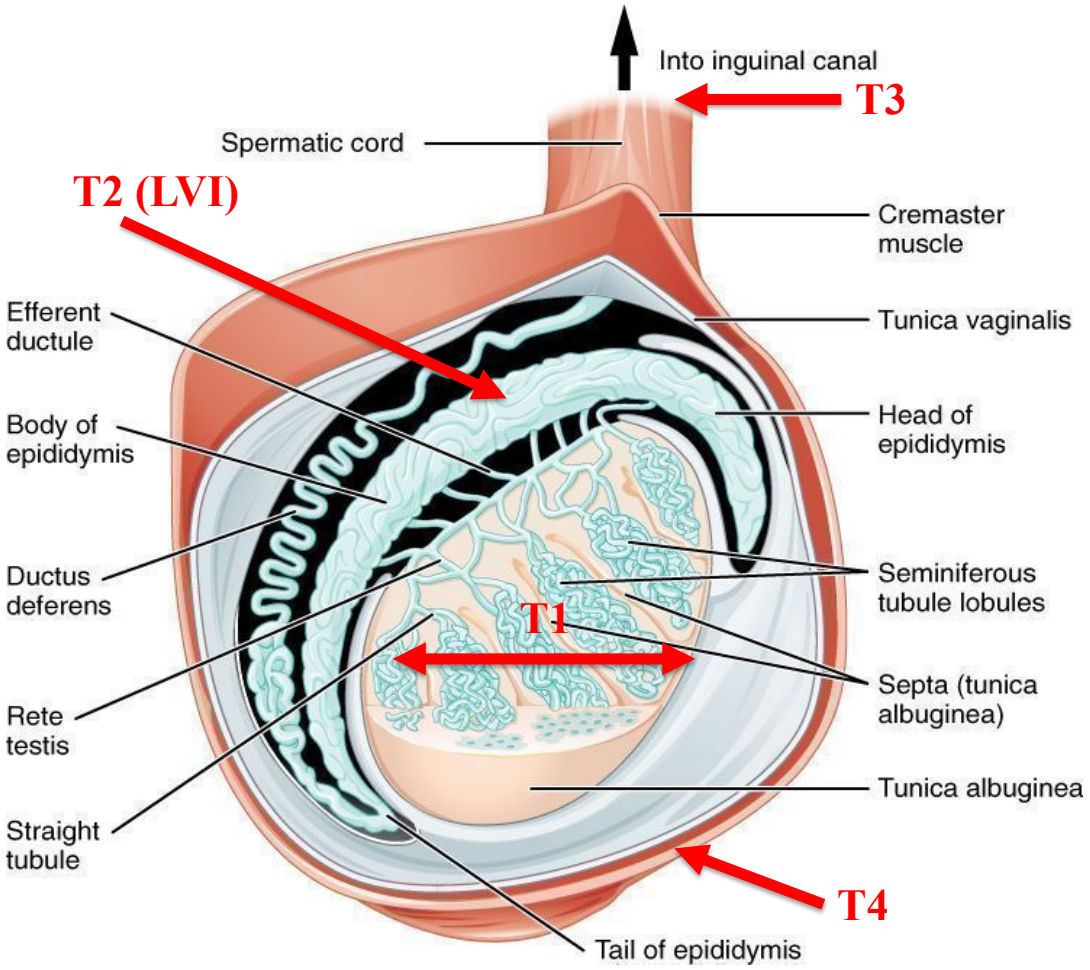
Tumour Markers

1.Onco-fetal Substances		2.Cellular Enzymes
AFP – (Alfafetoprotein)	**HCG – (Human Chorionic Gonadotropin)**	**1. LDH (Lactate dehydrogenase)**
Normal:<16 ngm / ml Half Life: 5 to 7 d Raised AFP : Pure embryonal ca Teratocarcinoma Yolk sac Tumour Combined Tumour	Has α and β polypeptide chain Normal: < 1 ng / ml Half Life: 24 to 36 hours Raised β HCG - 100 % - Choriocarcinoma 60% - Embryonal ca 55% - Teratocarcinoma 25% - Yolk Cell Tumour 7% - Seminomas	N=105 - 333 IU/L metastatic seminoma- 80% and metastatic nonseminoma-60% of patients **2.PLAP** Elevated -50% of seminomas at presentation (half-life of 24 hours).

Management of the primary tumor

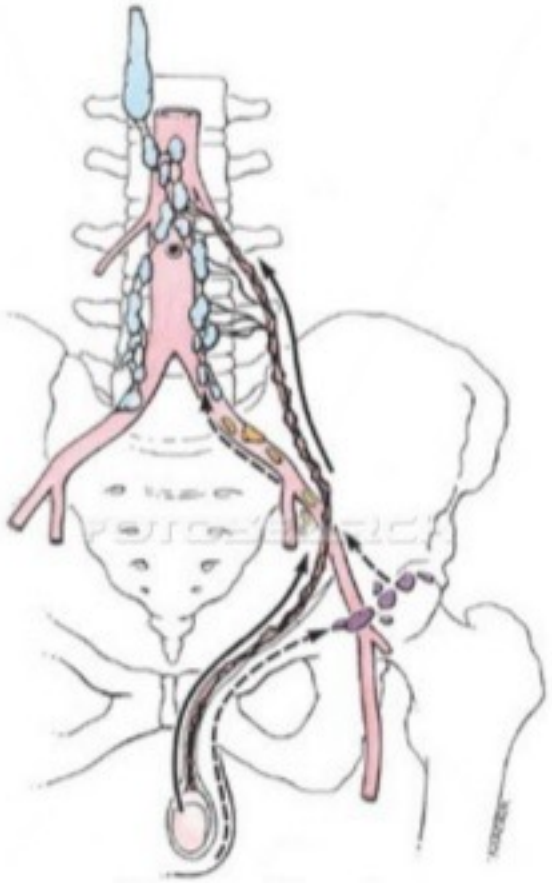
➔ Radical orchidectomy
➔ Should be carried before any further treatment (except emergency situation)

➔ Inguinal incision !!!
➔ No scrotal violation !!!!



Lymphatic Drainage

- **Right testis:** along the IVC →inter-aortocaval region → pre-aortic & para-aortic lymph nodes, with possible cross-over within the retroperitoneum
- **Left testis:** →Preaortic and para-aortic lymph nodes around the left renal hilum → inter-aortocaval nodes mostly without cross-over
- Retroperitoneal lymph nodes are located anterior to the T11 to L4 vertebral bodies concentrated at the L1–L3 level
- Nodal spread to **ipsilateral iliac chain is** ~3%
- **Scrotal skin:** lymphatics drain into the inguinal and external iliac nodes.



Baseline work-up

- Marqueurs + LDH after surgery !!!

- CT-scan thoraco-abdo total
- Thoracic CT could be omitted in seminoma without infradiaphragmatic M+
- Cerebral MRI in choriocarcinoma / High HCG

- **No indication of ^{18}FDG-PET in baseline staging !!!!**

AJCC 7th Edition

pTX	**Primary tumor cannot be assessed.**
pT0	No evidence of primary tumor (e.g., histologic scar in testis).
pTis	Intratubular germ cell neoplasia (carcinoma *in situ*).
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis.
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis.
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion.
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion.

NX	**Regional lymph nodes cannot be assessed.**
N0	No regional lymph node metastasis.
N1	Metastasis with a lymph node mass ≤2 cm ; or multiple lymph nodes, none >2 cm in greatest dimension.
N2	Metastasis with a lymph node mass >2 cm but not >5 cm ; or multiple lymph nodes, any one mass >2 cm but not >5 cm in greatest dimension.
N3	Metastasis with a lymph node mass >5 cm in greatest dimension.

M0	**No distant metastasis.**
M1	Distant metastasis.
M1a	Nonregional nodal or pulmonary metastasis.
M1b	Distant metastasis other than to nonregional lymph nodes and lung.

Required in post-operative setting !!!!

Serum Tumor Markers (S) Required for Staging	
SX	Marker studies not available or not performed.
S0	Marker study levels within normal limits.
S1	LDH <1.5 × N *and* hCG (mIu/ml) <5,000 *and* AFP (ng/ml) <1,000.
S2	LDH 1.5–10 × N *or* hCG (mIu/ml) 5,000–50,000 *or* AFP (ng/ml) 1,000–10,000.
S3	LDH >10 × N *or* hCG (mIu/ml) >50,000 *or* AFP (ng/ml) >10,000.

Post-orchiectomy staging of metastatic seminoma and non-seminoma according to AJCC/UICC and IGCCCG classification

Clinical stage	TNM (AJCC/UICC)			Serum tumour markers (S) to be determined after orchiectomy				IGCCCG prognostic group
	T[a]	N	M	S	LDH	HCG	AFP (ng/ml)	
IS	T_{any}	N0	M0	S1	<1.5xN and	<5000 and	<1000	Good
				S2	1.5–10xN or	5000–50 000 or	1000–10 000	Intermediate
				S3	>10xN or	>50 000 or	>10 000	Poor
IIA	T_{any}	N1 (≤2 cm)	M0	S0	Normal	Normal	Normal	Good
				S1	<1.5xN and	<5000 and	<1000	
IIB	T_{any}	N2 (>2–5 cm)	M0	S0	Normal	Normal	Normal	Good
				S1	<1.5xN and	<5000 and	<1000	
IIC	T_{any}	N3 (>5 cm)	M0	S0	Normal	Normal	Normal	Good
				S1	<1.5xN and	<5000 and	<1000	
IIIA	T_{any}	N_{any}	M1a	S0	Normal	Normal	Normal	Good
				S1	<1.5xN and	<5000 and	<1000	
IIIB	T_{any}	N1-3	M0	S2	1.5–10xN or	5000–50 000 or	1000–10 000	Intermediate
		N_{any}	M1a					
IIIC	T_{any}	N1-3	M0	S3	>10xN or	>50 000 or	>10 000	Poor
		N_{any}	M1a	S3	>10xN or	>50 000 or	>10 000	Poor
			M1b	S_{any}	Any level	Any level	Any level	Poor
	Primary mediast EGGCT	N_{any}	M_{any}	S_{any}	Any level	Any level	Any level	Poor

[a]Primary retroperitoneal EGGCT is staged like TGCT (T_{any}).

IGCCC – SEMINOMA

IGCCC GOOD

Seminoma (90% of cases)	*All of the following criteria:*
5-year PFS 82% 5-year survival 86%	• Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH

IGCCC INTERMEDIATE

Seminoma (10% of cases)	*All of the following criteria:*
5-year PFS 67% 5-year survival 72%	• Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH

No poor risk in seminoma

IGCCC – NON SEMINOMA

IGCCC GOOD

Non-seminoma (56% of cases)	***All of the following criteria:***
5-year PFS 89% 5-year survival 92%	• Testicular/retroperitoneal primary • No non-pulmonary visceral metastases • AFP < 1000 ng/mL • hCG < 5000 IU/L (1000 ng/mL) • LDH < 1.5x ULN

IGCCC INTERMEDIATE

Non-seminoma (28% of cases)	---
5-year PFS 75%	• Testicular/retroperitoneal primary • No non-pulmonary visceral metastases
5-year survival 80%	*And any of the following criteria:* hCG 5000–50 000 IU/L or LDH 1.5–10x ULN

IGCCC POOR

Non-seminoma (16% of cases)	***Any of the following criteria:***
5-year PFS 41% 5-year survival 48%	• Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10 000 ng/mL or • hCG > 50 000 IU/L (10 000 ng/mL) or • LDH > 10x ULN

Seminoma Stage 1

80% of patients with seminoma
Survival rate 99%

Prognostic Factors for Relapse in Stage I Seminoma Managed by Surveillance: A Pooled Analysis

- Pooled Data of 638 patients(Princess Margaret Hospital, Danish Testicular Cancer Study Group, Royal Marsden Hospital, and Royal London Hospital)
- Median follow-up -7.0 years
- Multivariate predictors for relapse:

  1) tumor size > 4 cm and

  2) invasion of rete testis

  – If tumor < 4 cm then age less than 30 independent risk factor

Rete testis and >4cm size
Considered as risk factor of relapse

"Long-term outcome of postorchiectomy surveillance for Stage I testicular seminoma."

- Prospective, single-arm.
- N=88
- 20% rete testis invasion, 45% >4cm. Median F/U 12.1 years, 3 lost to follow-up
- Relapse-free rate: 5-years 83%, 10-years 80%, 15-years 80%
- Relapse site: 88% (15/17) below diaphragm.
- Predictor for relapse: invasion of rete testis (HR 3.5, p= 0.03)

Warde et al; JCO 2002
Choo et al; IJROBP 2005

Seminoma Stage 1

	Stage I
First line	Low risk* Preferred : • Surveillance Alternatively : ▪ Carboplatin x 1 (AUC 7) ▪ Radiotherapy (20 Gy) High risk# Preferred: • Surveillance • Carboplatin x 1 (AUC 7) Alternatively: • Radiotherapy (20 Gy)

12% relapse

Surveillance only in **Compliant** patients !!!
Discuss adjuvant based on risk factors
BUT 99% survival independent of strategy

	Surveillance	Carboplatine	Adjuvant RT
% of relapse	20	3-4	4
Median time to relapse	14 mths	9 mths	4% at 5y
Location	Retroperitoneal	Paraaortic nodes	Distant mets
5-y specific survival	99.3%	99-100%	99-100%

Our advice :
Surveillance if possible, sparing overtreatment !!!

Seminoma Stage 2

	Stage IIA Nodes 1-2cm
First line	▪ BEPx3 (or EPx4) ▪ Radiotherapy

Chemotherapy

Prospective, non-randomized.
72 pts (18-Stage IIA, 54-Stage IIB)
Median f/u 71 m

- 4 cycles of cisplatin + etoposide
- 3 cycles of BEP (bleomycin, etoposide, cisplatin).

83% achieved CR, 17% PR.
5-yr PFS 100% and 87% for Stage IIA and IIB. 5-yr OS 95%
Conclusion: Chemotherapy is a highly effective and well-tolerated treatment for patients with stage IIA or IIB seminoma

(Spanish Germ Cell Cancer Group Garcia-Del-Muro X, J Clin Oncol. 2008 Nov 20;26(33):5416-5421.)

Radiotherapy

Disease specific survival rate 97-100%
Recurrence rate <10%

94 patients
RT to para-aortic and high ipsilateral iliac LNs
Median F/U 5.8 years

	Stage IIA (n=66)	Stage IIB (n=21)
Dose	30 Gy/ 15#	36 Gy/18#
6-year RLF	95%	89%

Toxicity: Grade 3 nausea 8-10%; no late toxicity
Conclusion: RT for Stage IIA-B seminoma, with reduced portals, yields excellent tumor control and no late toxicity

(Classen J, J Clin Oncol. 2003 Mar 15;21(6):1101-6.)

5-y OS 95-99%

ESMO Guidelines

Seminoma Stage 2B/C-3

	Stage IIB/IIC/III
First line	▪ BEPx3-4 (VIPx3-4)

Stade II B-C (If node>2cm)

Relpase with RT= 30%

➔ **Chemotherapy = standard**

- 3 BEP ou 4 EP

Stade III (If distant lesion)

➔ **Chemotherapy = standard**

- 3 BEP ou 4 EP if Good IGCCC
- 4 BEP ou 4 EP if Intermediate IGCCCC

ESMO Guidelines

Seminoma Surveillance

Table 1 Clinical Stage I Seminoma: Surveillance After Orchiectomy

	Year (at month intervals)				
	1	2	3	4	5
H&P[1,2]	Every 3–6 mo	Every 6–12 mo	Every 6–12 mo	Annually	Annually
Abdominal ± Pelvic CT	At 3, 6, and 12 mo	Every 6–12 mo	Every 6–12 mo	Every 12–24 mo	
Chest x-ray	As clinically indicated, consider chest CT in symptomatic patients.				

If Recurrence, treat according to extent of disease at relapse

Table 2 Clinical Stage I Seminoma: Surveillance After Adjuvant Treatment (Chemotherapy or Radiation)

	Year (at month intervals)				
	1	2	3	4	5
H&P[1,2]	Every 6–12 mo	Every 6–12 mo	Annually	Annually	Annually
Abdominal ± Pelvic CT	Annually	Annually	Annually	------	
Chest x-ray	As clinically indicated, consider chest CT in symptomatic patients.				

If Recurrence, treat according to extent of disease at relapse

[1]Serum tumor markers are optional.
[2]Testicular ultrasound for any equivocal exam.

NCCN

Seminoma: Residual disease

- **Patients with complete response ➔ follow-up**

- **In case of residual tumour,**

  < 3 cm ➔ Surveillance

  > 3cm ➔ FDG-PET 6 weeks after ending chemotherapy

  If negative PET scan ➔ Follow-up only.

  If positive PET scan ➔ Surgical resection preferred

Non-seminoma Stage 1

Excellent survival rate (98-100%)

- 371 patients
  - 28% relapse
  - 72% spared further treatment
  - survival >99%

- 223 patients
  - 26% relapse
  - 74% spared further treatment
  - Survival 100%

Zuniga, 2009, Kollmansgerger, 2009

Vascular invasion

Absence = Low risk

➔ 20% of relpase

Presence = high risk

➔ 40-50% of relapse

Clinical stage I Non-seminoma

	Stage I
First line	Vascular invasion absent Preferred: • Surveillance Alternatively: ▪ 1-2xBEP ▪ RPLND (rarely) Vascular invasion present Preferred: ▪ 1-2xBEP ▪ Surveillance Alternatively: ▪ RPLND (rarely)

20% will relapse with metastatic disease
➔ 80% do not need treatment

50 % will relapse with metastatic disease
➔ 50% do not need treatment

Option 1: 2 BEP eliminate risk of resurgence
Option 2: Observation and 3 cycles of BEP for patients who will recur is an alternative

98-99% survival independent of strategy

Our advice :
Surveillance if possible, sparing overtreatment !!!

Clinical stage II/III Non-seminoma

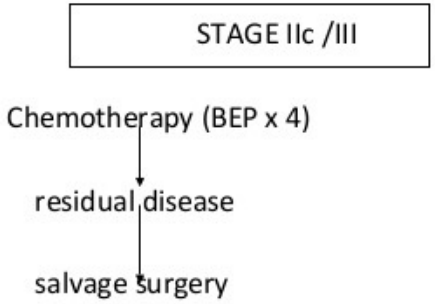
	Stage IИIII Good
First line	▪ BEPx3 (EPx4)

3 BEP (or 4 EP)

Clinical stage II/III Non-seminoma

	Intermediate	Poor
First line	▪ BEPx4 ▪ VIPx4	▪ BEPx4 ▪ VIPx4

4 BEP (or 4 VIP)



Note: - Radiation therapy only for palliation in metastatic disease.

Reference	Regimen(Cycles)	N	CR, %	DFS, %
De Wit 1995*	BEP (4) PveB/BEP (4)	118 116	72 76	NR NR
De Wit 1998*†	BEP (4) VIP (4)	38 46	82 80	79 85
Nichols 1998	BEP (4) VIP (4)	141 145	60 63	64 60

†Trial performed exclusively in nonseminoma, intermediate-risk patients.

Residual disease: non-seminoma

- Evaluation by imaging after 4-8 weeks post last cycle of chemotherapy
- If complete response (normal marker, no ≥ 10mm lymph node, no other mets)
  ➔ Follow-up
- If residual ≥ 10mm lymph node or other distant lesion (Liver or lung !!!)
  ➔ Resection

In case of <90% of radiological regression
- 45% have necrosis/fibrosis
- 45% have teratoma
- 6-8% will have viable carcinoma

Good IGCCCG
In case of viable tumor <10%
➔ no adjuvant therapy

Intermediate/poor IGCCCG
In case of >10% viable tumor
➔ Consolidation chemo (2 VIP)
➔ Or Surveillance (?)

Stage 1 non-seminoma

Table 5 Clinical Stage IA, NSGCT: Active Surveillance

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 2 mo	Every 3 mo	Every 4–6 mo	Every 6 mo	Annually
Abdominal ± Pelvic CT	Every 4–6 mo	Every 6–12 mo	Annually	---	---
Chest x-ray[2]	At mo 4 and 12	Annually	Annually	Annually	Annually

FOLLOW-UP FOR NONSEMINOMA

Table 7 Clinical Stage IB NSGCT: Treated with 1–2 Cycles of Adjuvant BEP Chemotherapy

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 3 mo	Every 3 mo	Every 6 mo	Every 6 mo	Annually
Abdominal ± Pelvic CT	Annually	Annually	---	---	---
Chest x-ray[2]	Every 6–12 mo	Annually	---	---	---

Follow-up

Procedure	Year 1	Year 2	Year 3-5	Year 6-10
Physical exam	4 times	4 times	2-4 times	Once/year
Tumor markers	4 times	4 times	2-4 times	Once/year
Chest X-ray	4 times	4 times	2-4 times	Once/year
Abdominal CT	2 times	1-2 times	1 time	As clinically indicated

Chemotherapy toxicity

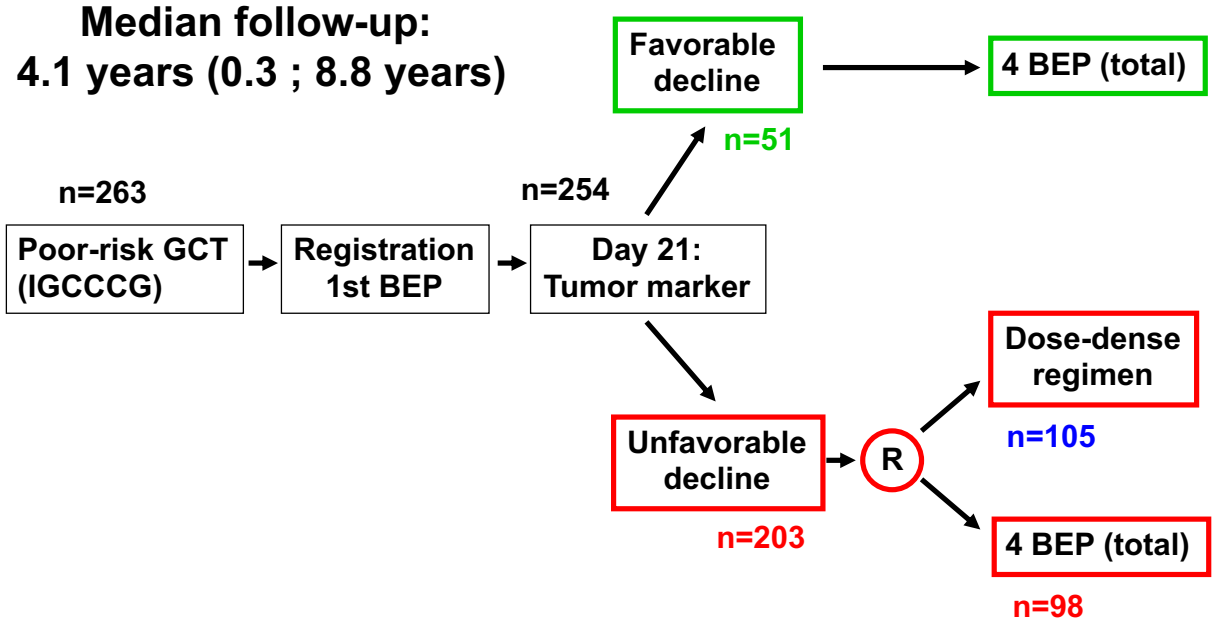
- Hair loss 100%
- Neutropenia 100%
  - ➔ GMCSF
  - ➔ Repeat cycle every 3 weeks independent of leukocyte count
- Transient infertility likely: cryopreservation necessary
- **Cardiovascular effects:**

  hypertension, Raynaud's phenomenon, myocardial ischaemia / infarction, Cardiovascular accident (up to 15 years later; HR x 2-7)
- Renal impairment: 20-30% most sub-clinical
- Anxiety and depression; Weight gain
- Ototoxicity 23-30%
- Neuropathy 30%
- **Second cancer development (HR x 1.5)**

Intermediate/poor risk trials
Unmet medical need

- To date, no therapy be superior to 4 BEP
- POOR RISK: Clinical trial !!!.

GETUG 13 study design



Fizazi et al ESMO 2013

GETUG 13: dose dense regimen

BEP × 1

Cisplatin 20 mg/m²/d d1-5
Etoposide 100 mg/m²/d d1-5
Bleomycin 30 u/w

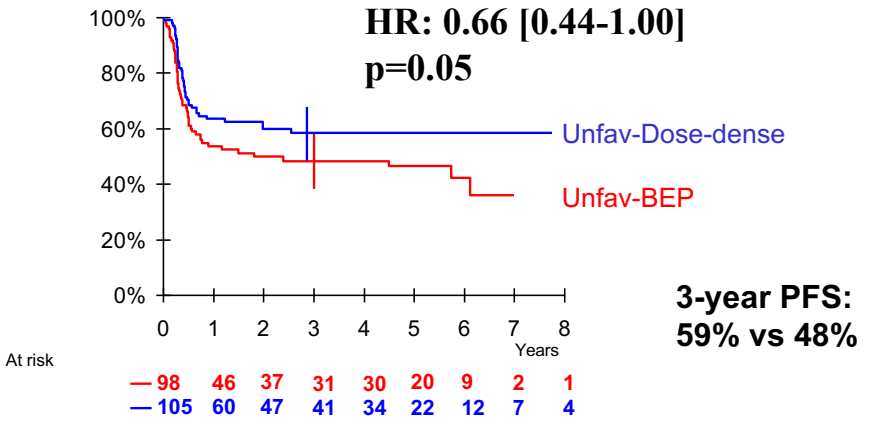
Paclitaxel-BEP + Oxaliplatin
+ G-CSF
/ 3 weeks × 2 cycles

Paclitaxel 175 mg/m² d1
BEP as above
Oxaliplatin 130 mg/m² d10
G-CSF 263 µg/d (excepted chemo days)

Cisplatin, Ifosfamide, Bleomycin
+ G-CSF
/ 3 weeks × 2 cycles

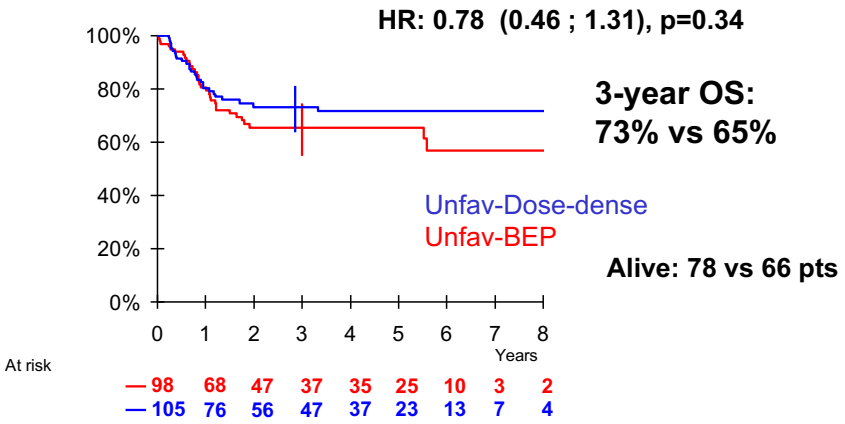
Cisplatin 100 mg/m² d1
Ifosfamide 2g/m² d10,12,14
Mesnum
Bleomycin 25 U/d d10-14
(continuous IV)
G-CSF as above

Progression-free survival



3-year PFS:
59% vs 48%

Overall survival



3-year OS:
73% vs 65%

Alive: 78 vs 66 pts

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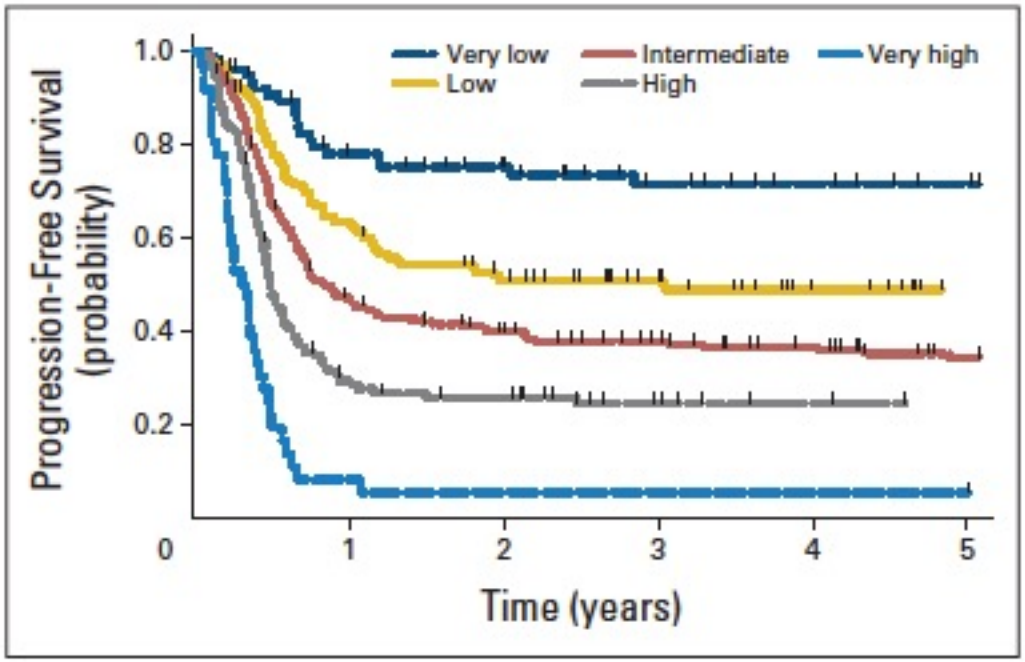
ORIGINAL REPORT

Prognostic Factors in Patients With Metastatic Germ Cell Tumors Who Experienced Treatment Failure With Cisplatin-Based First-Line Chemotherapy

The International Prognostic Factors Study Group

Table 4. Prognostic Score for Patients With Nonseminoma and Seminoma

Parameter	Score Points 0	1	2	3	Score
Primary site	Gonadal	Extragonadal	—	Mediastinal nonseminoma	
Prior response	CR/PRm−	PRm+/SD	PD	—	
PFI, months	> 3	≤ 3	—	—	
AFP salvage	Normal	≤ 1,000	> 1,000	—	
HCG salvage	≤ 1,000	> 1,000	—	—	
LBB	No	Yes	—	—	
Score sum (values from 0 to 10)					
Regroup score sum into categories: (0) = 0; (1 or 2) = 1; (3 or 4) = 2; (5 or more) = 3					
Add histology score points: pure seminoma = −1; nonseminoma or mixed tumors = 0					
Final prognostic score (−1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk)					



LBB = Liver, brain, bone

Conventional-dose Salvage Regimens

• PEI	Cisplatin	20 mg/m^2	Day 1 - 5	
	Ifosfamide	1.2 g/m^2	Day 1 - 5	Motzer 1990
	Etoposide	75 mg/m^2	Day 1 - 5	
• VeIP	Cisplatin	20 mg/m^2	Day 1 - 5	
	Ifosfamide	1.2 g/m^2	Day 1 - 5	Loehrer 1998
	Vinblastine	0.11 mg/kg	Day 1 +2	
• TIP	Cisplatin	20 mg/m^2	Day 2 - 6	
	Ifosfamide	1,2 g/m^2	Day 2 - 6	Motzer 2000
	Paclitaxel	175-250 mg/m^2	Day 1	

Repeated every 21 days for 4 cycles

Salvage chemotherapy regimens

VeIP (VLB-Ifo-CDDP) en 1ère ligne de rattrapage -- 124 patients :

- 50 % advanced
- 60 % : absence de RC initiale
- 25 % : extra gonadiques

Résultats :

- 23 % DFS à 2 ans
- 75 % neutropénies G III - IV
- 3 décès toxiques

→ VIP ou VeIP = référence actuelle

Late relapse

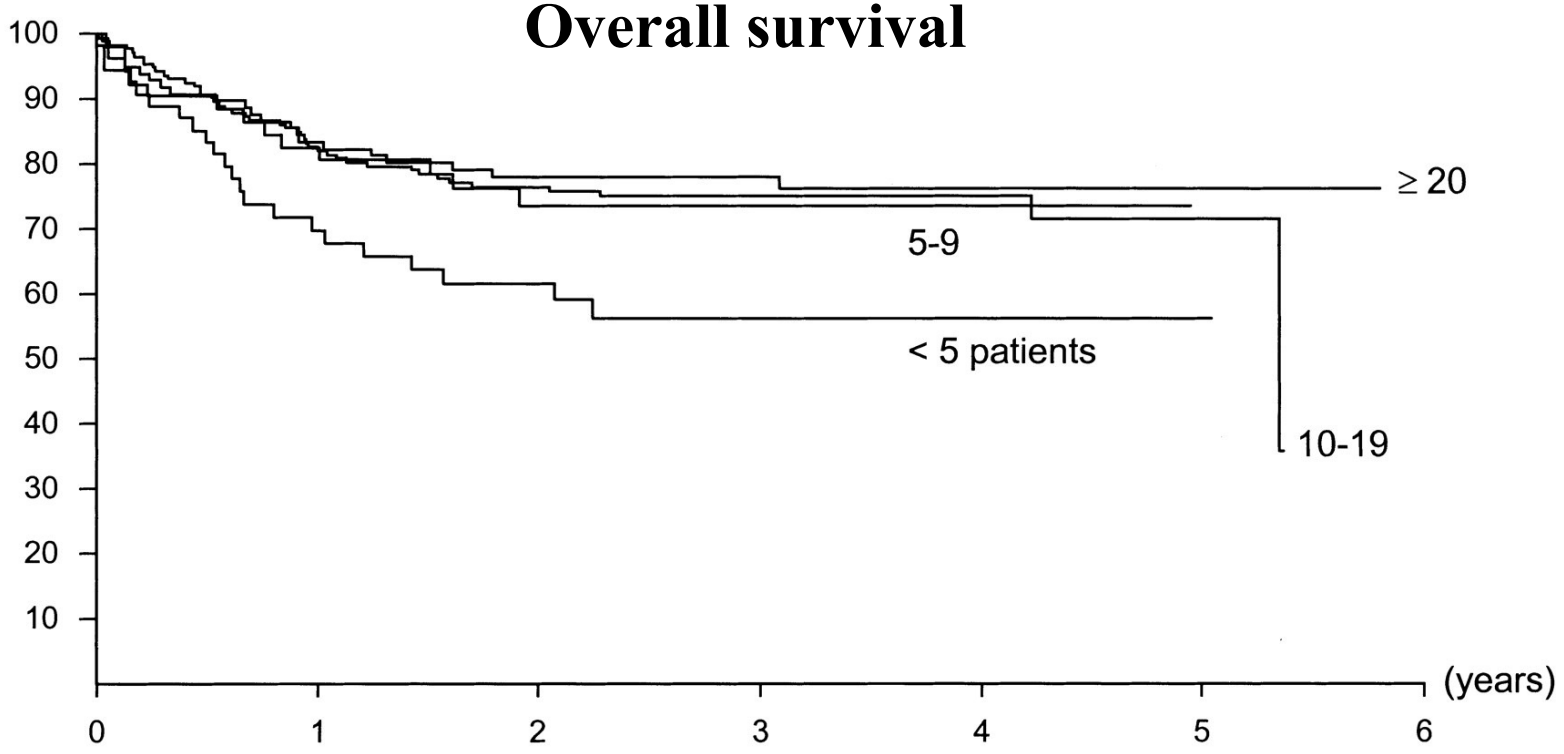
- Of patients destined to recur, > 90% will occur within 24 months
- Late relapse = recurrence > 24 months from achieving disease-free status
- Have been documented to occur out to 32 years after CR
- These recurrences are usually chemoresistant
  - ➔ should not be treated with chemotherapy or high-dose regimens
  - ➔ Surgical resection represents the best therapeutic

Sanctuary sites

- Testicle
  - chemotherapy insufficient to eradicate primary in testicle

- Brain
  - risk factors for CNS involvement:
    - pure choriocarcinoma (can bleed !)
    - hCG > 100,000
    - large volume pulmonary metastases

Overall survival



O	N	Number of patients at risk :					Total Accrual
22	55	35	25	12	8	1	<5
13	52	42	28	18	4	0	5-9
44	174	138	114	74	28	4	10-19
22	99	78	60	49	33	11	>=20

Collette L et al. JNCI J Natl Cancer Inst 1999;91:839-846